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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,431	11/26/2003	Ning Hu	01992.007US1	6228

53137 7590 01/12/2009

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EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
01/12/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,431	HU ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28,30,31,33,40-42 and 47-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28, 30-31, 33, 40-42 and 47-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The response dated 11-14-08 is acknowledged.

Claims included in the prosecution are 1-28, 30-31, 33, 40-42 and 47-71.

Upon consideration, the rejections involving EP are withdrawn.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-28, 30-31, 33, 40-42 and 47-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/13816 in combination with Tardi (US 2003/0124181).

WO 99 discloses a method of loading camptothecins using a pH gradient at a higher temperature, which is same as instant method. The lipids used include DSPC, cholesterol and phosphatidylglycerols. The buffer used is citrate buffer which is more than 5 mM. The lipid to camptothecin ratios are from 5:1 to 100:1 (abstract, pages 10-15, 18, Example 2 and claims). Although in examples, WO uses citric acid at 50 mM concentration, in view of WO's teachings that it can be higher than 5 mM, it would have been obvious to one of ordinary skill in the art to vary the molarity with the expectation of obtaining the best possible results. What is lacking in WO is the loading of active agents other than camptothecins, such as claimed anthracyclines and vinca alkaloids.

Tardi while disclosing liposomal compositions containing various active agents teaches that therapeutic agents which can be loaded using pH gradients comprise one more ionizable moiety such that the neutral form of the ionizable moiety allows the drug to cross the liposome membrane and conversion of the moiety to charged form causes the drug to remain encapsulated within the liposomes. Tardi teaches that the ionizable moieties comprise amine, carboxylic acid and hydroxyl groups. Among the active agents taught by Tardi are camptothecins, vinca alkaloids such as vinblastine, and vincristine and anthracycline antibiotics such as doxorubicin (0080-0081). Tardi further teaches dehydrating the liposomes and the use of cryoprotectants (claims).

The use of the liposomes of WO to load active agents such as anthracycline antibiotics and vinca alkaloids would have been obvious to one of ordinary skill in the art since Tardi teaches that any ionizable active agent having an amine, carboxyl and hydroxyl functional groups can be loaded using pH gradients and those compounds include camptothecins, anthracyclines and vinca alkaloids.

WO does not teach the use of sphingomyelin in the preparation of the liposomes, since it is a commonly used lipid in the liposome formations, it would have been obvious to one of ordinary skill in the art to use this lipid with a reasonable expectation of success.

Applicant's arguments have been fully considered, but are not persuasive. Applicant mainly focuses on Tardi's teachings and argues that Tardi does not teach the preparation of any liposomes using the quenching step. Further according to applicant, the final liposomes prepared by Tardi maintain a low pH in the internal aqueous space that helps keep the drug loaded in the liposomes. These arguments are not persuasive.

The examiner recognizes the method of Tardi is slightly different from the method of WO. However, both methods are directed to loading of the ionizable drugs using pH gradients and WO teaches such a step. Tardi is combined since WO does not teach drugs other than camptothecins and Tardi teaches the equivalency between camptothecins and claimed anthracyclines and vinca alkaloids. Since all of them are ionizable compounds, one of ordinary skill in the art would be motivated to use the method of WO to load even anthracyclines and vinca alkaloids. Applicant has not shown any unexpected results by using the method taught by WO for loading these drugs.

With regard to WO, applicant argues the following:

"Gradient loading using a lower concentration of citric acid produces a final liposome with a small amount of residual acid present, since most of the internal acid is consumed by the therapeutic agent within the liposome. Accordingly a liposome loaded at a lower concentration of citric acid (e.g. 50 mM) would only require a small amount of base to quench the residual acid present after loading. When a higher concentration of citric acid (e.g., greater than 60 mM) is utilized during a gradient loading process, the amount of therapeutic agent present in the final liposomes is not great enough to neutralize a majority of the residual acid. Accordingly when liposomes are loaded at a higher acid concentration there is a significantly greater amount of residual acid remaining in the liposomes following loading. Accordingly, it is submitted one skilled in the art would not have had a reasonable expectation that liposomes could be loaded at a higher concentration of acid (e.g., greater than 60 mM) and subsequently quenched as recked in the instant claims after viewing the examples in WO 99/13816, since one skilled in the art would have appreciated that the amount of residual acid in a liposome loaded at a higher concentration of citric acid (e.g., greater than 60 mM) would have been significantly higher than the amount of residual citric acid present in a liposome loaded at a concentration of 50 mM as discussed in the Examples of WO 99/13816. Additionally, one skilled in the art would have believed that gradient loading using a high concentration of citric acid would produce a final liposome with a higher concentration of therapeutic agent in the liposome than would be produced by gradient loading at a lower concentration of citric acid. Accordingly one skilled in the art would have known that gradient loading using a higher concentration of acid would produce a final liposome that is potentially less thermodynamically stable, i.e. a liposome wherein the therapeutic agent is more likely to leak or escape from the liposome. As discussed above, Tardi teaches that it is critical to maintain low pH in the internal aqueous space after active loading of the liposome in order to keep the therapeutic agent trapped inside. One skilled in the art would have understood that the teaching of Tardi would have been more relevant for liposomes loaded at higher gradients, since these liposomes contain more therapeutic agent and thus, are more likely to leak if the pH gradient is quenched. For this additional reason, it is submitted that it would not have been obvious to one of ordinary

skill in the art to vary the molality (by increasing the concentration of citric acid) with the expectation of obtaining the best possible results, as suggested by the Examiner. In fact, it is submitted that one skilled in the art would have more likely assumed that quenching liposomes that were gradient loaded at a high concentration of citric acid would have produced liposomes that were unstable (i.e. liposomes where the therapeutic agent would leak from the liposome) in light of the discussion in Tardi."

These arguments are not persuasive. First of all, instant claims do not recite any specific amounts of therapeutic agent and therefore, arguments that higher concentration of concentration is utilized in the loading process and when a higher concentration of citric acid is utilized during a gradient loading process, the amount of therapeutic agent present in the final liposomes is not great enough to neutralize a majority of the residual acid are not persuasive. Furthermore, it is within the skill of the art to recognize this stated parameter. Secondly, instant lower limit is 60 mM and WO teaches 50 mM and applicant has not shown any unexpected results obtained by this change in the concentration.

Applicant's arguments that the inclusion of claim 7 is an error are not persuasive since sphingomyelin is known in the art as a liposome forming lipid. Applicant's arguments that the inclusion of claim 49 is an error are not persuasive since the prior art clearly indicates that methylamine is a commonly used base in liposome technology. Applicant's arguments that the inclusion of claims 52-57 is an error are not persuasive since Tardi clearly shows the use of cryoprotectants (claims).

3. Claims 7 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/13816 in combination with Tardi as set forth above, further in view of Webb (5,814,335) of record.

The teachings of WO and Tardi have been discussed above. What is lacking in these references is the use of sphingomyelin as the liposome-forming lipid. The use of

sphingomyelin however, would have been obvious to one of ordinary skill in the art since Webb teaches that sphingomyelin containing liposomes are stable and have extended circulation time (abstract). Neither EP nor WO teaches the change of the pH of the external medium by using methylamine. The use of methylamine to change the pH of the external medium would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since Webb teaches the creation of pH gradient using methylamine (columns 7 and 8).

Applicant's arguments have been fully considered, but are not persuasive. The examiner has already addressed applicant's arguments regarding WO and Tardi. Applicant provides no specific arguments regarding the use of sphingomyelin taught by Webb. Applicant argues that Webb uses methylamine for a significantly different function. This argument is not persuasive since methylamine is a base which is commonly used for changing the pH while loading drugs into the liposomes and it is within the skill of the art to use any base including methylamine with the expectation of obtaining similar pH changes and applicant has not shown any unexpected results by using methylamine.

4. Claims 52-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/13816 in combination with Tardi (US 2003/0124181) as set forth above, further in view of Clerc (5,939,096).

The teachings of Tardi and WO have been discussed above.

Clerc while disclosing a method of drug loading by pH gradient teaches that liposomes can be dehydrated for storage in the presence of cryoprotectant sugars (col.

8, lines 9-15). It would have been obvious to one of ordinary skill in the art to use cryoprotectants and dehydrate liposomes since they can be stored in that state as taught by Clerc.

Applicant's arguments have been fully considered, but are not persuasive. The examiner has already addressed applicant's arguments regarding WO and Tardi. Applicant provides no specific arguments regarding the use of cryoprotectants taught by Clerc.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-28, 30-31, 33, 40-42 and 47-71are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 30-

31 and 35-64 of U.S. Patent No. 6,740,335 in combination with Tardi (US 2003/0124181). Although the conflicting claims are not identical, they are not patentably distinct from each other because both patented claims and instant claims are drawn to the process of loading agents using pH gradients. Instant claims are generic with respect to the active agents loaded whereas the patented claims recite specific camptothecin compound. However, it would have been obvious to one of ordinary skill in the art to load any active agent using a pH gradient with a reasonable expectation of success since Tardi teaches that any ionizable active agent having an amine, carboxyl and hydroxyl functional groups can be loaded using pH gradients and those compounds include camptothecins, anthracyclines and vinca alkaloids. Patented claims do not recite the concentration of the acid while loading the active agent and instant mM amounts therefore, are deemed to be anticipated by the claims in the patent.

Applicant's arguments have been fully considered, but are not persuasive. The essence of applicant's arguments is that WO 99/13816 is a counter part of US 6,740,335 and therefore, the same arguments as above are applicable. The examiner has already addressed those arguments. The rejection therefore, is maintained.

In view of the amendment to the claims in the copending application, the double patenting rejection over the claims in 10/723,610 is withdrawn.

7. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore /
Primary Examiner, Art Unit 1612

GSK